CSPI Center for Science in the Public Interest

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Docket Management Branch (HFA 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Approval of Subtherapeutic Uses in Livestock
Docket No. 99P 0485

These comments are submitted partly in response to comments submitted on June 8, 1999, by the Animal Health Institute (AHI) regarding the Center for Science in the Public Interest (CSPI) petition to rescind approval of subtherapeutic uses of human-use antibiotics in livestock (Docket Number 99P-0485).

The AHI asserts that there is no new evidence that has not been reviewed by the Food and Drug Administration (FDA) regarding the safety of antibiotics used subtherapeutically.[1] Contrary to that claim, there is significant new evidence, which was outlined in the CSPI petition, as well as a new FDA standard of safety that necessitates reevaluation of the safety of human-use antibiotics in livestock feed. That safety standard, articulated by the FDA in November 1998, states that:

> This draft guidance document announces that FDA now believes it is necessary to evaluate the human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs.[2]

The impact on humans of pathogens that are resistant to antibiotics due to subtherapeutic uses of antibiotics has not been evaluated for the antibiotics approved as feed additives.

The significant new scientific evidence that indicates an adverse public-health impact of subtherapeutic antibiotic use in livestock has been the basis for the World Health Organization (WHO) to recommend that antibiotics used in human medicine not be allowed to be used subtherapeutically in livestock. The European Union (EU) subsequently banned the use of all antibiotics used in or related to those used in human medicine.

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[1] The AHI paper cites several studies that claim that the subtherapeutic use of antibiotics in livestock does not endanger human health. Those studies are discussed in Appendix 1.

[2] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, *Draft Guidance for Industry: Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*, November 1998.

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The CDC has reviewed that new evidence and has found that "The recent EU action to ban antimicrobials used in human medicine as growth promotants is scientifically justifiable, consistent with WHO recommendations, and protects the public health." A 1998 National Academy of Sciences report commissioned by the U.S. Department of Agriculture and the FDA concluded that "there is a link between the use of antibiotics in food animals, the development of bacterial resistance to these drugs, and human disease." A 1999 report by the General Accounting Office has stated that resistant strains of three specific organisms that cause illness or disease in humans -- *Salmonella, Campylobacter,* and *E. coli* -- are linked to the use of antibiotics in animals.

The FDA should immediately implement measures to rescind the approvals of antibiotics for subtherapeutic use in livestock. The CSPI petition asks for the FDA to review seven approved antibiotics (penicillin, tetracycline, erythromycin, virginiamycin, tylosin, lincomycin, and bacitracin) based on the ample evidence that antibiotic resistance can develop in bacteria that cause food poisoning. Because of that risk, the FDA cannot assure that there is reasonable certainty of no harm from the subtherapeutic use of those antibiotics.

As its top priorities, the FDA should initiate proceedings to revoke the approval that allows the subtherapeutic use of **virginiamycin** and should hold the hearings called for by the 1977 Notices of Opportunity for Hearings on **tetracycline** and **penicillin**.

The subtherapeutic use of virginiamycin in livestock poses a grave public-health threat because it can result in bacteria that are resistant to the related (human use) drug Synercid. Synercid was approved on September 21, 1999, and is the last therapeutic option for serious antibiotic-resistant bloodstream infections. Because of the use of virginiamycin on the farm, even before Synercid had been approved in people Synercid-resistant bacteria had been isolated from animals, abattoir workers, and other people. Individuals colonized with enterococci resistant to Synercid had been found in the Netherlands and Germany.[3,4] In the U.K., Synercid-resistant enterococci that are also vancomycin-resistant were found in a hospital patient.[5] That finding is particularly worrisome, because there is no other antibiotic that will effectively treat an infection caused by such multi-resistant bacteria. In the U.S., a recent CDC study showed that poultry (obtained from supermarkets) and people were colonized by Synercid-resistant enterococci.[6] Synercid resistance has not led to treatment failure in

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[3] van den Bogaard AE, Mertens P, London NH, Stobberingh EE, "High prevalence of colonization with vancomycin and pristinamycin-resistant enterococci in healthy humans and pigs in the Netherlands: is the addition of antibiotics to animal feed to blame?" *Journal of Antimicrobial Chemotherapy*, 1997;40:454-6.

[4] Witte W, "Medical consequences of antibiotic use in agriculture." *Science*, 1998;279:996-7.

[5] Woodford N, Palepou M-F, Johnson AP, Chawick PR, Bates J, "Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci." *Lancet*, 1997;350:737-8.

[6] Angulo F, Marano N, Mackinson C, Wang Y, Sokolow R, DeBess E, Koehler J, Benson J, Hill B, McDonald C, "Isolation of quinupristin-dalfopristin-resistant *Enterococcus faecium*

humans yet, because, until this month, Synercid had not been approved for people. It is likely that it will occur shortly, now that Synercid will be used more widely in people.

Subtherapeutic uses of penicillin and tetracycline have been banned in almost all other developed countries for decades with no adverse consequences to animal health. Continued use of those antibiotics can select for multi-drug resistant strains of bacteria, which are becoming more prevalent in the US. For example multidrug-resistant *Salmonella typhimurium* DT104 has increased in prevalence in the U.S. from less than one percent in 1979 to 34 percent of *Salmonella typhimurium* isolates.

AHI asserts that eliminating subtherapeutic uses of antibiotics in feed would increase the cost of livestock production. Even though the financial consequence of banning those uses is not relevant to the decision of whether those antibiotics are safe, animals can be raised economically without antibiotics. In addition to the evidence presented in the CSPI petition, an abstract presented at the September 1999 American Society for Microbiology meeting demonstrates that in Denmark, where poultry producers voluntarily stopped all use of antibiotics for growth promotion, poultry production has become more profitable.[7] (Appendix 2) The cost savings of not using antibiotics in feed outweighed the slight increase in the amount of feed needed to raise chickens to slaughter weight. In 1998, the therapeutic use of antibiotics did increase slightly. Twenty five flocks were treated for infections with 24 kg of antibiotic. In previous years one or two flocks needed such treatment. But before the voluntary ban, growers would have used 1,500 kg of antibiotics annually as growth promoters. Overall, the profit to Danish farmers increased by 25 cents per 100 broilers.

In conclusion, we emphasize the need for the FDA to protect the public health by banning the subtherapeutic use in livestock of antibiotics important in human medicine. The petition asks the FDA to take action on seven such antibiotics. We suggest that the FDA prioritize by focusing on virginiamycin, penicillin, and tetracycline first.

Sincerely,

Patricia Lieberman

Patricia Lieberman, Ph.D.
Staff Scientist

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from human stood specimens and retail chicken products in the United States ." *Interscience Conference on Antimicrobial Agents and Chemotherapy*, American Society for Microbiology, September 26-29, 1999, San Francisco, CA.

[7] Emborg H-D, "Chicken production is profitable without antibiotic growth-promoters." *Interscience Conference on Antimicrobial Agents and Chemotherapy*, American Society for Microbiology, September 26-29, 1999, San Francisco, CA.

Appendix 1: Comments on AHI's comment

The AHI comments (June 8, 1999) cite studies that have either been discredited or superseded or were not peer reviewed. The AHI cites a paper by Cherubin that states, "the role of low-concentration, growth-promoting antibiotic feed supplements has been much discussed but never has been delineated or proven. In fact, these supplements probably are totally irrelevant to the development of antibiotic resistance in salmonella."[1] The author of that 1981 paper disputes that *Salmonella* is a zoonotic pathogen, and suggests that it is transmitted largely from person to person. That conclusion is wrong, as it is now widely recognized that most cases of salmonella infections in people in the developed world come from animal sources.

A paper by DuPont and Steele was cited as concluding that "it does not appear that the banning of drugs as feed additives, with concomitant unrestricted use of these agents for the treatment of both animals and people, would favorably influence the problems of antimicrobial resistance and salmonellosis in human populations."[2] The evidence the authors cite to back up that claim comes from the United Kingdom, where after 1969 antibiotics that were used in human medicine were not allowed to be added routinely to livestock feed. However, even the authors acknowledged that farmers evaded the restrictions by obtaining antibiotic feed additives through veterinarians. Other authors also have stated that antibiotics still were often used subtherapeutically.[3,4] Thus, the fact that the U.K. did not see a significant reduction in resistance among *Salmonella* and other types of bacteria may have been due partly to the fact that, in actuality, there never was an effective ban (in addition to the fact that no other restrictions on veterinary and human use were implemented).

Dupont and Steele further claimed that it is impossible to determine what proportion of the problem of antibiotic resistance is due to subtherapeutic use of antibiotics versus therapeutic uses. It is difficult to assess what proportion of the problem is due to subtherapeutic antibiotic use, but that does not mean that the subtherapeutic use is safe. In fact, the authors themselves acknowledged that "animals used in food production do serve as a reservoir of salmonellae that are potentially capable of causing infections in humans. A practice that encourages the propagation of *Salmonella* strains resistant to antimicrobial agents is of public health concern." The authors also acknowledged that "it is true that the bacterial flora of domestic animals fed certain antibiotic-enriched feed acquires impressive patterns of antimicrobial resistance."

Perhaps the best way to illustrate that the subtherapeutic use of antibiotics causes antibiotic resistance among bacteria that can infect people is to look at antibiotics that only are used subtherapeutically in animals, and not in people or animals for therapy. For example, bacteria in people are becoming resistant to virginiamycin, an antimicrobial that has not been approved for use in humans but that is used subtherapeutically in animals. Moreover, bacteria that are resistant to virginiamycin also are resistant to the related drug, Synercid, that will soon be approved for use in people. In Germany, where Synercid also is not used in humans but virginiamycin is used subtherapeutically in livestock, Synercid-resistant enterococci have been

detected in humans.[5] A study in the Netherlands revealed that 30% of healthy people were colonized with virginiamycin-resistant *E. faecium* in their fecal flora.[6]

Other evidence that the subtherapeutic use of antibiotics in livestock can lead to resistance in bacteria that infect humans comes from the experience in Germany with the growth promoter nourseothricin. Although nourseothricin has been used solely for growth promotion in swine and was never approved for people, nourseothricin resistance was found in *E. coli* in people.[7] Though that resistance has not yet proven harmful to people, Germany's experience with nourseothricin provides striking evidence that subtherapeutic use in animals can foster the growth of antibiotic-resistant bacteria that can be passed to people.

Contrary to claims by the AHI, the January 1, 1986, Swedish ban on antibiotic growth promoters has led to a dramatically lower use of antibiotics in livestock production. An article by Mudd *et al.* in a non-peer-reviewed trade publication, cited in the AHI comments, asserts that since the 1986 ban usage of antimicrobials has increased.[8] Those authors' conclusion are misleading for a number of reasons. First, the report lists antimicrobial usage from 1986 (after the ban) to 1996. The appropriate comparison would have used data from before the ban.

Second, Mudd *et al.*'s conclusion is based largely on four selected antibiotics, and not on all growth-promoting antimicrobials. A close look at the selection reveals a strong bias. Two of the antibiotics selected (fluoroquinolones and pleuromutilins) were not even on the market at the time of the ban, therefore *any* sales of those antibiotics would indicate an increase in usage after the ban. Additionally, the antibiotics (nitroimidazoles and trimethoprim-sulphonamides) that were replaced by fluoroquinolones and pleuromutilins were *not* included in the analysis. Hence, corresponding decreases in sales data for those antibiotics were not included in the analysis.

The authors included penicillin, in their analysis. But in Sweden, penicillin is used primarily for treating mastitis in dairy cows, and is not given to promote growth. The increase in penicillin use reflects an increased rate of mastitis. Therefore, information about penicillin use is largely irrelevant to evaluating the effectiveness of a ban on subtherapeutic antibiotics.

The fourth antibiotic, and the only appropriate choice for study, was tetracycline, which was used as a growth promoter prior to the ban. Tetracycline use in animals declined from 6,585 kg in 1986 to 2,733 kg in 1996, a decline of almost 60%. An even more appropriate comparison is usage prior to the ban to usage in 1986 or later. Thus, in 1984, 12,955 kg of tetracyclines were used; that's almost twice as much as in 1986 and almost five times as much as in 1996.[9]

An analysis of all subtherapeutic antibiotic use in livestock in Sweden shows that, when corrected for potency, a 70 percent decrease was seen from the mean usage in 1980-84 to 1996.[10]

Perhaps the most compelling evidence supporting the success of Sweden's ban is lower levels of antibiotic resistance among *E. coli* compared to countries that have not banned antibiotics for growth promotion. A study by van den Bogaard *et al.* compares antimicrobial

usage and antimicrobial resistance in *E. coli* in pigs in Sweden and the Netherlands.[11] That report found 14 percent of isolates resistant to macrolide antibiotics among pigs in Sweden compared to 88 percent of isolates from pigs in the Netherlands. That reflects lower usage of macrolides in Sweden (1803 kg) compared to the Netherlands (62,282 kg).

The AHI charges that the EU's ban on the use of four antibiotics was not based on sound science. In fact, the EU reviewed reports from the Scientific Committee for Animal Nutrition (SCAN) and additional information from member nations. After reviewing a large body of evidence and expert opinion, the EU concluded that subtherapeutic uses pose a public-health risk. Since the ban, the EU's Scientific Steering Committee has recommended that the use of *any* antibiotic, not just those used in human medicine, be phased out of animal feed.[12]

References

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7. Hummel R, Tschäpe H, Witte W, "Spread of plasmid-mediated nourseothricin resistance due to antibiotic use in animal husbandry." *Journal of Basic Microbiology*, 1986;26:461-6.

8. Mudd AJ, Lawrence K, Walton J, "Study of Sweden's model on antimicrobial use shows usage has increased since 1986 ban." *Feedstuffs*. October 26, 1998, p. 18.

9. Ministry of Agriculture, Food and Fisheries, *The Swedish Model of Animal Production*, Stockholm, Sweden; 1998.

10. Ibid.

11. van den Bogaard A, London N, Driessen C, Stobbering E, "The effect of growth promoters on the resistance in faecal indicator bacteria of pigs." In: *ICAAC*; 1998;11998.

12. European Union, "EU scientists recommend reduction of antimicrobials use." Press release, June 1, 1999 at <http://www.eurunion.org/news/press/1999/1999034.htm>.

Appendix 2

American Society for Microbiology
28-Sep-99

Chicken Production Is Profitable without Antibiotic Growth-Promoters

Library: MED
Keywords: CHICKEN FARM ANTIBIOTIC RESISTANCE FOOD
Description: Results from Denmark show that chicken meat can be produced profitably without the use of antimicrobial growth promoters.
9/27/1999

CHICKEN PRODUCTION IS PROFITABLE WITHOUT ANTIBIOTIC GROWTH PROMOTERS

Presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy
September 26-29, 1999, San Francisco, California
Contact: Jim Sliwa ñ (202) 942-9297 ñ jsliwa@asmusa.org
[September 25-29: (415) 978-3640]

EMBARGOED UNTIL MONDAY SEPTEMBER 27, 1999, 9:30 A.M. PDT

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Results from Denmark show that chicken meat can be produced profitably without the use of antimicrobial growth promoters (AGPs). On February 15, 1998 the Danish poultry industry voluntarily stopped all use of AGPs for broilers. The industry feared this would result in losses due to decreased productivity and increased disease problems. Instead, the industry has gained from the withdrawal of AGPs because of a significant decrease in the overall consumption of antimicrobials, resulting in an overall increased profit of 25 cents per 100 birds.

Reduced exposure of consumers to resistant bacteria from chicken meat will also be the result of withdrawal of AGPs.

The Danish Poultry Council provided all data about productivity, and the statistics are based on data from almost all flocks slaughtered in Denmark in 1998, totaling more than 100 million birds.

Danpo A/S, a subsidiary of Scandinavian Poultry, has provided disease statistics. In 1998, they slaughtered just under 50 million birds and their data show that the withdrawal of AGPs did not result in major disease problems in the flocks. The work is presented at the 39th ICAAC conference in San Francisco and will be presented at Monday, September 27th, 1999 at 9:30 to 11:00 AM.

In May 1995, the Danish Minister of Food, Agriculture and Fisheries banned the use of the antimicrobial growth promoter (AGP) avoparcin in Denmark. The ban was imposed when it was documented that avoparcin was associated with occurrence of vancomycin resistance, an antimicrobial used in human medicine. In January 1998, a second AGP virginiamycin was banned, and finally, on February 15, 1998 the broiler industry voluntarily discontinued all use of AGPs.

The Danish Poultry Council has recorded productivity data for the commercial Danish broiler production since 1975. These data provide valuable information on the effects of the withdrawal of AGPs on productivity and profitability. Based on data from 1998 the mean feed consumption at 42 days of age did increase from 1.78 kg feed to 1.82 kg per kg live bird after withdrawal of AGPs and has remained above 1.81 kg. The slaughter weight at 42 days of age initially decreased from 1,960g to 1,930g, but has since increased, and in 1999 the mean weight at 42 days is well above 2,000g, Table 1.

Data from the central database and from Danpo A/S show no increase in the general morbidity of commercial broiler flocks since AGPs were withdrawn. But as expected there has been a modest increase in the number of flocks suffering from the Clostridium perfringens related diseases, necrotic enteritis and chronic hepatitis.

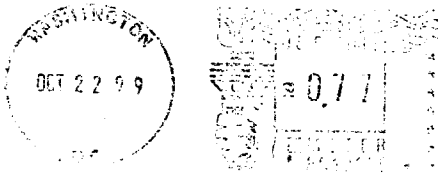
In, 1998 Danpo produced about 1,700 flocks. The first year after the AGPs were withdrawn, necrotic enteritis and chronic hepatitis were diagnosed in 25 flocks compared to 1-2 flocks per year when AGPs were used. A total of 24 kg amoxicillin (active compound) was used to treat the outbreaks. Alternatively, without the voluntary stop the Danpo flocks would have used 1,500 kg active compound of AGPs, primarily avilamycin but also bacitracin.

The profitability of the withdrawal of AGPs is based on figures from Danpo A/S.
Costs:
- Necrotic enteritis was diagnosed in 25 out of 1,700 Danpo flocks. Splitting the costs equally on all broilers slaughtered at Danpo resulted in an average cost of 4 cents per 100 broilers.
- The increased mean feed consumption at 42 days of age increased the production cost per 100 broilers by 114 cents
- All together an extra cost per 100 broilers of 118 cents.

Benefits:
- The exclusion of AGPs from the feed reduced the costs per 100 broilers with 143 cents on average.

The overall profit increased by 25 cents per 100 broilers on average.

In conclusion, the Danish experience shows that it is possible for the Danish broiler producers to compete internationally after the withdrawal of AGPs. The additional and significant benefit for the consumer is a reduced risk of exposure to resistant bacteria from broilers.



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